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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,785	03/19/2004	Frits Goedegebuur	GC793-3	7768

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EXAMINER	
RAGHU, GANAPATHIRAM	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,785	GOEDEGEBUUR ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 6 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 8-25* is/are withdrawn from consideration.

5)☒ Claim(s) *26-28* is/are allowed.

6)☒ Claim(s) *6 and 7* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

In response to the Final Office Action dated 10/17/2007, applicants' filed an RCE received on 10/31/07 is acknowledged. Said RCE amended claims 6 and 7 and added new claims 26-29. Claims 1-29 are pending, claims 1-5 and 8-25 are withdrawn as they are drawn to non-elected inventions and thus claims 6, 7 and 26-29 are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn- Claim Rejections: 35 USC § 112, written description

Previous rejection of claims 6-7 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants' amendments to the claims

Withdrawn- Claim Rejections: 35 USC § 102

In view of Applicant's amendment, the previous rejection of claims 6-7 under 35 U.S.C. 102(b) as being anticipated by Radford, et al. (A) is withdrawn.

Claim Objections

Claim 29 is objected to under 37 CFR 1.75(c), as being of improper dependent form for

failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 29 is improperly dependent as it is outside the scope of claim 28, as claim 28 recites "...said variant consists...".

Claim Rejections: 35 USC § 112, second paragraph

Claim 6 and claim 7 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites the phrase "hybridizes", but does not recite conditions under which the hybridization must occur. Nucleic acids which hybridize under one set of conditions may not hybridize under other conditions. Thus the scope of the claims is unclear. A perusal of the specification, on pages 15-16 describes exemplary hybridization conditions, however claim as written do not recite the specific conditions the applicants' intend to encompass. Clarification and correction is required.

Maintained- Claim Rejections: 35 USC § 112 Enablement

Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant *H. jecorina* CBH1 cellulase, wherein said variant comprises a substitution or deletion at a position corresponding to amino acid residue T66 of the mature *H. jecorina* CBH1 protein and further said variant *H. jecorina* CBH1 cellulase has cellulolytic activity and has at least 95% sequence identity to SEQ ID NO: 2, the specification does not reasonably provide enablement for any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any substitution corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 2, wherein said *H. jecorina* CBH 1 cellulase

has cellulolytic activity and said variant is encoded by a nucleic acid sequence that hybridizes to a nucleic acid sequence having about 80% sequence identity to SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim (mere recitation of sequences from prior art in the specification does not overcome the deficiency in the scope of the claims).

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 6 and 7 are so broad as to encompass any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 2, wherein said *H. jecorina* CBH 1 cellulase has cellulolytic activity and said variant is encoded by a nucleic acid sequence that hybridizes to a nucleic acid sequence having about 80% sequence identity to SEQ ID NO: 1. Thus, the claimed cellulases have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 2 and 80% sequence identity to SEQ ID NO: 1. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants of *H. jecorina* CBH 1 cellulase protein as broadly encompassed by the claims. Since the amino acid sequence of a protein

encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to a variant *H. jecorina* CBH1 cellulase, wherein said variant comprises a substitution or deletion at a position corresponding to amino acid residue T66 of the mature *H. jecorina* CBH1 protein and further said variant *H. jecorina* CBH1 cellulase has cellulolytic activity and has at least 95% sequence identity to SEQ ID NO: 2, but provides no guidance with regard to making and using variants of *H. jecorina* CBH1 cellulase i. e., any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 2, wherein said *H. jecorina* CBH 1 cellulase has cellulolytic activity and said variant is encoded by a nucleic acid sequence that hybridizes to a nucleic acid sequence having about 80% sequence identity to SEQ ID NO: 1. In view of the great breadth of the claims, the amount of experimentation required to determine a use for the full scope of the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompasses any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 2, wherein said *H. jecorina* CBH 1 cellulase has cellulolytic activity and said variant is encoded by a nucleic acid sequence that hybridizes to a nucleic acid sequence having about 80% sequence identity to SEQ ID NO: 1, because the specification does not establish: **(A)** the desired CBH 1 activity of all polypeptides including variants of *H. jecorina* CBH1; **(B)** regions of the protein/polynucleotide structure which may be modified without affecting the activity of encoded polypeptide; **(C)** the general tolerance of the polypeptide and the polynucleotide encoding to modification and extent of such tolerance; **(D)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological

function; and **(E)** the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants' have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including polypeptides and encoding polynucleotides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 2 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 2, wherein said *H. jecorina* CBH 1 cellulase has cellulolytic activity and said variant is encoded by a nucleic acid sequence that hybridizes to a nucleic acid sequence having about 80% sequence identity to SEQ ID NO: 1, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the prior rejection of claims 6 and 7 under 35 U.S.C. 112 for enablement be withdrawn, applicants', provide the following argument.

(A) Claims as amended recite variant *H. jecorina* CBH 1 cellulase...encoded by a nucleic acid sequence that hybridizes to a nucleic acid sequence having about 80% sequence identity to SEQ ID NO: 1.

(B) Applicants' have identified possible sites involved in the stability of the CBH1 enzyme in three different ways... and the specification teaches a variant CBH1 polypeptide comprising a substitution or deletion at a position corresponding to one or more residues.

(C) Because only an enabling disclosure is required, applicant need not describe all actual embodiments...although the variants would need to be assayed for activity and the present specification provides means to conduct the assay.

Applicants' arguments have been considered and the following body of scientific publication supports the basis for rejection.

(A) (B) & (C) Reply: Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The claims as written when given the broadest interpretation reads on extremely large number of variants CBH1 cellulase, wherein said cellulase comprises a substitution or deletion at the position corresponding to T66 of SEQ ID NO: 2 and encoded by a nucleic acid sequence that hybridizes to a nucleic acid sequence having about 80% sequence identity to SEQ ID NO: 1. Furthermore, said variant comprises any substitution (any other 19 amino acids), corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 2 and further comprising a substitution at a position corresponding to residue Q186 (E), S195 (A/F), E239S, G242 (H/Y/N/S/T/D/A) and P412 (T/S/A) and said variants encoded by a nucleic acid having about 80% sequence identity to SEQ ID NO: 1 and hence claims as written encompass nucleic acid molecules comprising random changes to the polynucleotide sequence of SEQ ID NO: 1; 20% change in identity translates to 298 random nucleotide changes in SEQ ID NO: 1 having 1491 nucleotides. Applicants' claims in

fact encompass any variant that would hybridize to any of the vast number of nucleic acid and this includes proteins encoded by nucleic acid molecules having even more than 298 nucleotide changes in SEQ ID NO: 1.

While methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan, producing variants as claimed requires that one of ordinary skill in the art know or be provided with guidance for the selection of which, of the infinite number of variants, have the activity. The guidance provided by the applicants is limited to the specific amino acid residues of SEQ ID NO: 2 and not to any random changes in the encoding polynucleotide of SEQ ID NO: 1, said polynucleotide having about 80% sequence identity to SEQ ID NO: 1. For the rejected claims, this would clearly constitute **undue** experimentation. Guo et al., (PNAS, 2004, Vol. 101 (25): 9205-9210) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (p 9206, paragraph 4). Guo et al., (*supra*) further show that the percentage of active mutants for multiple mutations appears to be exponentially related to this by the simple formula $(.66)^{X}$ X 100% where **x** is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 80% sequence identity to the polynucleotide of SEQ ID NO: 1 allows up to 298 mutations within the 1491 nucleotides of SEQ ID NO: 1 encoding a polypeptide of 497 amino acids of SEQ ID NO: 2. For argument sake, even if one assumes only 1/3-1/2 of the 298 nucleotide changes result in amino acid changes, the number of likely amino acid changes will be still around 100-149 amino acid changes and, thus, only $(0.66)^{100}$ X 100% - $(0.66)^{149}$ X 100% equivalent to **9.0×10^{-17} % - 1.3 x**

10^{-25} % of random mutants having 80% sequence identity to SEQ ID NO: 1 would be active. Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a reasonable number of active mutants within hundred thousand inactive mutants (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish). But finding a few mutants within several trillions or more, as in the claims to 80% sequence identity, would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Applying this estimate to the instant protein, a functional equivalent thereof with 80% sequence identity, as recited in Claims 6 and 7, an extremely low number of active mutants will be present among an enormously large number of inactive mutants and as such screening for these active mutants would be burdensome and undue experimentation when there is no guidance provided in the specification.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Claim 29 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

2. Claim 6 and claim 7 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

4. Claims 26-28 are allowable.

Applicants must respond to the rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Claims 6 and 7 are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
Art Unit 1652
Dec. 07, 2007.

/Rebecca Prouty/
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